REMARKS

Claims 22-33 and 49-94 are pending in the subject application. Claims 22-24, 26, 28, 30, 32, 33, 52, 53, and 79 are amended. Claims 76, 90, and 91 are canceled. The amendments to the claim are supported by the specification as filed, and no new matter is presented. Favorable reconsideration in light of the remarks which follow is respectfully requested.

1. 35 U.S.C. §112 Rejections

Claims 22-33 and 49-92 are rejected under 35 U.S.C. §112, second paragraph as being indefinite.

The Office asks what is meant by "solubility of the second amphiphilic component ----- is at least ten times greater than the solubility of the first amphiphilic lipid component", and asserts that "the phospholipids are insoluble in water". Applicants respectfully traverse.

Applicants claim, in claim 22, a method for producing a preparation wherein a first amphiphilic lipid component and a second amphiphilic component are selected such that the solubility of the second amphiphilic component in the pharmaceutically acceptable suspending medium is at least ten times greater than the solubility of the first amphiphilic lipid component in said medium. As set forth in the specification, the suspension medium is usually water or a different polar, generally aqueous medium (see e.g. [0081]). However, Applicants respectfully submit that the amphiphilic lipid components do possess solubility in the medium, which can be water. The Office makes an assertion that phospholipids are insoluble in water, which is not correct.

Phospholipids are lipids that, in their simplest form, are composed of glycerol bonded to two fatty acids and a phosphate group. The resulting compound contains a region (the fatty acid component) that is fat soluble and a region (the charged phosphate group) that is water soluble.

Applicants' claim recitation that "the solubility of the second amphiphilic component in the pharmaceutically acceptable suspending medium is at least ten times greater than the

solubility of the first amphiphilic lipid component in the medium" is clear as written. Applicants respectfully request reconsideration and withdrawal of this rejection.

The Office further asserts that it is unclear what applicant intends to convey by "further selected such that the permeation capability of the vesicles increases disproportionally or nonlinearly under increasing pressure".

Applicants respectfully submit that, as set forth in the specification, permeability is a linear function of the driving pressure for liposomes. On the other hand, transfersomes, which differ from liposomes, possess a permeability that increases disproportionally or nonlinearly as driving pressure increases. (See [0015]) Thus, this feature further distinguishes the present transfersome preparations from previous liposomal preparations.

The Office asks where the vesicles are permeated/in a subject or in vitro. Applicant has amended the claim to indicate that the permeability is through the skin or mucous membrane of a mammal.

The Office further asserts that the term, "liquid droplets" is confusing. While Applicants respectfully disagree, claim 1 has been amended for clarification to expedite prosecution. As set forth in the amended claim, the vesicles comprise liquid droplets suspended in the suspension medium. Each of the liquid droplets are provided with a sheath of one or more layers, the sheath comprising the first and second amphiphilic components. The active ingredient is contained in the liquid droplets, or in the sheath, or in both the liquid droplets and sheath.

Applicant has amended claim 23 to delete the phrase "for example".

Applicant has amended claim 24 to clarify how filtration under pressure, controlled mechanical whirling up, shearing, and comminuting are utilized. In particular, stability and/or permeation capability can be determined by such methods. In particular, filtration under pressure can be used to determine stability and permeation. Controlled mechanical whirling up, shearing, and comminuting are methods that are generally used to determine stability.

Applicant has amended claim 26 to correct the typographical error pointed out by the Office.

Applicant has amended claim 28 for clarification as requested by the Office.

Regarding claim 29, Applicant respectfully submits that the claim is clear as written. Claim 29 reads:

> The method of claim 22 wherein said amphiphilic components, either as such or dissolved in **a physiologically compatible solvent or solutizer**, which is miscible with a polar liquid or liquids, are combined with a polar pharmaceuticaly acceptable medium.

By wording the claim "a physiologically compatible solvent or solutizer", it is understood that this element is first introduced in this claim and was not previously introduced in claim 22.

Regarding claim 30, the second recitation of stirring has been deleted. With respect to rubbing, this has also been deleted to expedite prosecution.

The Office further asks what is the droplet which is formed in claim 32. Applicant respectfully submits that the claim is clear as written. Claim 32 depends from claim 22, which recites, in part, "producing a vesicle suspension by means of applying energy to the mixture, said vesicles comprising liquid droplets". Thus, the droplets are defined in claim 22. While Applicant disagrees with the rejection, applicant, nonetheless, has amended claim 32 for further clarification.

The Office further indicates that claim 33 is inconsistent with claim 22. While Applicants respectfully disagree, claim 33 has been amended for clarity and is consistent with claim 22.

Applicant has amended claim 52 to correct a typographical error pointed out by the Office.

The Office asserts that it is unclear what the permeation barrier is as recited in claim 53. While Applicant respectfully submits that it would be clear what a permeation barrier is in view of the specification, Applicant has amended claim 53 for further clarity.

Claim 76 has been canceled to expedite prosecution.

Claim 79 has been amended to correct a typographical error (claim 79 depends from claim 73 rather than claim 53) pointed out by the Office.

The Office asserts that the Markush members in claim 80 are not moieties and are not amphiphilic lipids. Applicants respectfully disagree. Contrary to the Office's assertion, the members of the group in claim 80 include amphiphilic lipid components. Further, the Office has offered no support for its statement otherwise.

The Office asserts that claim 90 is confusing. To expedite prosecution, Applicants have canceled claims 90 and 91.

Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C.§112 rejections based on the above remarks and amendments.

2. Double Patenting

U.S. Patent No. 6,165,500

Claims 53-91 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-35 of U.S. Patent No. 6,165,500 (US'500).

The Office asserts that "500 teaches the same transfersomes with same components". Applicants respectfully traverse.

Applicants claim in independent claim 53 a non-invasive method of using a preparation in the form of vesicles suspended in a liquid suspension medium by applying the preparation to a permeation barrier selected from the skin and mucous membranes of a mammal and allowing the

vesicles to transport at least one active ingredient for medicinal or biological purposes into and through the permeation barrier. As set forth, the vesicles comprise a sheath of at least one layer of amphiphilic carrier substance. The amphiphilic carrier substance comprises at least two physiochemically different amphiphilic components differing in their solubility in the liquid suspension medium by a factor of at least 10. The amphiphilic components are selected such that independently of their concentration, a solubilization of the vesicles does not occur, the permeation capability of the vesicles through barriers or constrictions in the skin or mucous membrane of a mammal increases disproportionally or nonlinearly under increasing pressure.

U.S. Patent No. 6,165,500 (US'500) describes transfersomes comprising a pharmaceutically acceptable lipid and a pharmaceutically acceptable surfactant contained in a pharmaceutically acceptable medium. According to claim 1, the total concentration of lipid in the medium is from about 0.1% to about 30% by weight, and the ratio of lipid to surfactant is from about 5.5:1 to about 1:500.

However, there is absolutely no teaching or suggestion anywhere in US'500 of a transfersome comprising at least two physiochemically different amphiphilic components differing in their solubility in the liquid suspension medium by a factor of at least 10 as set out in Applicants' claims. This comes purely from Applicants' disclosure. Nowhere in US'500 is the solubility of the lipid and surfactant in the pharmaceutically acceptable medium, much less the relationship between the solubility of the lipid and the surfactant, even considered.

Thus, it is respectfully submitted that the double patenting rejection of the present claims over US'500 should be reconsidered and withdrawn.

U.S.S.N. 10/357,618

Claims 22-33 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 69-87 and 101-103 of copending U.S.S.N. 10/357,618 (USSN'618).

With regard to this provisional double patenting rejection, Applicants submit that upon consideration and entry of the instant Amendment and Response, the provisional double patenting rejection will be the only rejection remaining in the instant application. Therefore, pursuant to M.P.E.P. §822.01, Applicants respectfully request that the provisional obviousness-type double patent application be withdrawn so that the instant application may proceed to allowance.

2. 35 U.S.C. 102 Rejections

Blume

Claims 22-30, 32, 49-50, 53-84, 87 and 92 are rejected 35 U.S.C. 102(b) over Blume et al of Record (Blume). Applicants respectfully traverse.

Blume describes lipid vesicles composed of phosphatidylcholine and polyoxyethylene-derivatives of phosphatidylethanolamine and their longevity after administration.

However, Blume at least fails to teach or suggest a method for producing a preparation for transporting at least one active ingredient through the skin or mucous membrane of a mammal comprising selecting a first amphiphilic lipid component and a second amphiphilic component such that the solubility of the second amphiphilic component in the pharmaceutically acceptable suspending medium is at least ten times greater than the solubility of the first amphiphilic lipid component in said medium, and wherein independently of the concentrations of the first and second amphiphilic components and the active ingredient, no solubilization of the vesicles in the suspension occurs, as set forth in independent claim 22.

Blume further fails to teach or suggest a non-invasive method of using a preparation in the form of vesicles suspended in a liquid suspension medium, the vesicles comprising a sheath of at least one layer of amphiphilic carrier substance, the amphiphilic carrier substance comprising at least two physiochemically different amphiphilic components differing in their solubility in the liquid suspension medium by a factor of at least 10, the amphiphilic components selected such that independently of their concentration, a solubilization of the vesicles does not occur, as set forth in independent claim 53.

Blume does not mention anything about the solubility of components forming the lipid vesicles. Blume further does not mention anything regarding the solubility of the components with respect to each other. Blume does not teach or suggest that the relationship between the solubility of the components with respect to each other should or could be taken into account in forming the described lipid vesicles.

Blume clearly does not expressly or inherently describe each and every element as set forth in Applicants' claims 22 or 53. Accordingly, claims 22 and 53 are clearly not anticipated by Blume. Claims 23-33, 49-52 and 53-92 depend from claims 22 and 53 and, likewise, are not anticipated by Blume. Reconsideration and withdrawal of the rejections is respectfully requested.

EP 0 475 160 (English equivalent US 6,165,500)

Claims 22-33 and 49-92 are rejected under 35 U.S.C. 102(b) over EP 0 475 160 (EP'160)(English equivalent US 6,165,500 "US'500). Applicants respectfully traverse for the same reasons as set forth above regarding US'500.

It is well established that a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). US'500 simply does not expressly or inherently describe each and every element of applicants claims 22 or 53.

US'500 at least fails to teach or suggest a method for producing a preparation for transporting at least one active ingredient through the skin or mucous membrane of a mammal comprising selecting a first amphiphilic lipid component and a second amphiphilic component such that the solubility of the second amphiphilic component in the pharmaceutically acceptable suspending medium is at least ten times greater than the solubility of the first amphiphilic lipid component in said medium, and wherein independently of the concentrations of the first and

second amphiphilic components and the active ingredient, no solubilization of the vesicles in the suspension occurs, as set forth in independent claim 22.

US'500 further at least fails to teach or suggest a non-invasive method of using a preparation in the form of vesicles suspended in a liquid suspension medium, the vesicles comprising a sheath of at least one layer of amphiphilic carrier substance, the amphiphilic carrier substance comprising at least two physiochemically different amphiphilic components differing in their solubility in the liquid suspension medium by a factor of at least 10, the amphiphilic components selected such that independently of their concentration, a solubilization of the vesicles does not occur, as set forth in independent claim 53.

US'500 does not say anything about the solubility of the lipid or the surfactant in the pharmaceutically acceptable medium, nor does US'500 say anything regarding the solubility of the lipid in comparison to the solubility of the surfactant. US'500 does not teach or suggest that the relationship between the solubility of the lipid and the surfactant should or could be taken into account in forming the described transfersomes. In fact, the only discussion of solubility in US'500 relates to droplet solubilization (abstract); transfersome solubilization (col. 54, lines 60-64); vesicle solubilization (col. 3, lines 52-54; Fig. 8; col. 58, lines 22-26; col. 57, lines 58-65; col. 50, lines 32-34); carrier solubilization/solubilization dose (col. 4, lines 50-54; col. 50, lines 54-55; col. 56, lines 60-63); fat-soluble vitamins (col. 7, line 55); transfersomes as carriers of fat-soluble biological agents (col. 52, lines 16-18); water soluble residue (col. 9, lines 4-5); water soluble tetraalkylammonium-ion (col. 14, line 18); that water and/or fat soluble substances can be incorporated/held in the transfersome (col. 4, lines 42-45; col. 4, lines 60-61; col. 50, lines 36-38); that lipids possess a water-soluble, polar, hydrophilic group (col. 6, lines 15-16); that edge active substances can provoke solubilization (lysis) (col. 7, lines 61-67); that edge active substances have a segment which is poorly water soluble (col. 11, lines 34-36); and with regard to carriers, poorly water-soluble substances in such case remain confined largely to the apolar region of a permeability barrier (such as in the epidermal membranes); agents which are highly soluble and can diffuse easily from the carriers can attain a distribution which is different from that of the carrier particles (col. 50, lines 18-23).

Accordingly, it is respectfully submitted that claims 22 and 53 are clearly not anticipated by EP'160 (US'500). Claims 23-33, 49-52 and 53-92 depend from claims 22 and 53 and, likewise, are not anticipated by EP'160 (US'500). Reconsideration and withdrawal of the rejections is respectfully requested.

3. 35 U.S.C. 103 Rejections

Claims 22-33 and 49-92 are rejected under 35 USC 103(a) over EP 0 475 160 (English equivalent US 6,165,500 "US'500). Applicants respectfully traverse for the same reasons as set forth above regarding US'500.

As set forth above, US'500 (and EP'160) does not teach or suggest a method of producing or using a preparation comprising a first amphiphilic lipid component and a second amphiphilic component, wherein the solubility of the second amphiphilic component in a pharmaceutically acceptable suspending medium is at least ten times greater than the solubility of the first amphiphilic lipid component in the medium. In fact, there is absolutely no mention of the solubility of either the lipid or the surfactant components in the pharmaceutically acceptable medium, much less a relationship between the solubility of the lipid and the solubility of the surfactant. This teaching comes purely from Applicants' present disclosure.

Accordingly, it is respectfully submitted that claims 22 and 53 are patentable over EP'160 (US'500). Claims 23-33, 49-52 and 54-92 depend from claims 22 and 53 and, likewise, are patentable over EP'160 (US'500). Reconsideration and withdrawal of the rejections is respectfully requested.

CONCLUSION

It is believed the application is in condition for immediate allowance, which action is earnestly solicited. Should the Examiner wish to discuss any of the amendments and/or remarks made herein, the undersigned attorney would appreciate the opportunity to do so.

If for any reason a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge or credit Deposit Account No. 04-1105 under order no. 58069 (47126).

Respectfully submitted,

Date: May 1, 2006

Lisa Swiszcz Hazzard (Reg. 44,368)
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, MA 02205
(617) 439-4444